DIETARY INTERVENTIONS TO CONTRAST THE ONSET AND PROGRESSION OF DIABETIC NEPHROPATHY:

A Critical Survey of New Data

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ABSTRACT

This article is a critical overview of recent contributions on the dietary corrections and the foods that have been claimed to delay or hinder the onset of diabetic nephropathy (DN) and its progression to end-stage renal disease. Innovative dietary and behavioral approaches to the prevention and therapy of DN appear the more captivating in consideration of the rather well established protocols for glucose and blood pressure control in use. In addition to restricted caloric intake to contrast obesity and the metabolic syndrome, adjustments in the patient's macronutrients intake, and in particular some degree of reduction in protein, have been long considered in the prevention of DN progression. More recently, the focus has shifted to the source of proteins and the content of glycotoxins in the diet as well as to the role of specific micronutrients. Few clinical trials have specifically addressed the role of those micronutrients associated with diet proteins that show the most protective effect against DN. Research on clinical outcome and mechanisms of action of such micronutrients appears the most promising in order to develop both effective intervention on nutritional education of the patient and selection of functional foods capable of contrasting the onset and progression of DN.

Key Words: Diabetes mellitus; nephropathy; diet; protein intake; advanced glycation end-products (AGEs); inflammation

INTRODUCTION

Diabetic nephropathy (DN), the leading cause of end-stage renal disease (ESRD) in the Western world, has reached a staggering incidence rate in the adult and elderly age groups. The burden of ESRD, both in terms of patient disability and financial costs, is steadily growing. In the USA, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) estimates that the adjusted incidence of ESRD, which was 80 per million in 1980, reached over 350 per million in 2009; what is more, the health care expenditure for ESRD patients has shown a rapid increase from 16 billion dollars to 42 billion dollars between 1998 and 2009 (Ahad et al., 2014). DN, a serious complication of both type 1 and type 2 diabetes mellitus (DM), is heralded clinically by microalbuminuria (20-199 µg/min), otherwise called "moderately increased albuminuria", as suggested by the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (KDIGO, 2013); microalbuminuria appears approximately 10 years after the onset of diabetes (*incipient DN*), often progresses to overt proteinuria (*overt DN*), and finally leads to ESRD (Mogensen, 1999). However, recent evidence indicates that decline of glomerular filtration rate (GFR) may develop independently of albuminuria or even in the absence of it, in both type 1 (Molitch et al., 2010) and particularly type 2 DM (Retnakaran et al., 2006), suggesting that loss of renal function might occur via two, possibly distinct pathways, albuminuric and nonalbuminuric (Pugliese, 2014).

In DM patients, several approaches are now employed to delay the inception of DN and to reduce its speed of progression. Prevention is aimed at putting off onset of DN in nonalbuminuric diabetic patients (primary prevention); progression to overt DN of microalbuminuric diabetic patients (secondary prevention); and progression to ESRD in macroproteinuric patients (tertiary prevention) (Gross et al., 2005). The current management scheme includes the following: strict glycemic control, anti-hypertensive drugs, lipid-lowering treatment, dietary adjustment, obesity

reduction, and changes in the individual activity pattern. The rationale for this combined therapeutic approach is to offset both major mechanisms that bring about diabetic glomerulosclerosis, i.e. long-term hyperglycemia and hypertension.

This article is a critical overview of recent contributions on the dietary corrections and the foods that have been considered to delay or hinder the onset of DN and its progression to ESRD. Innovative dietary and behavioral approaches to the prevention and therapy of DN appear the more captivating in consideration of the rather well established protocols for glucose and blood pressure control in use. The data collected should aim at identifying possible guidelines for dietary adjustment and restrictions, or specific supplementation consensus protocols deemed to be beneficial to offset the onset and progression of this diabetic complication.

CURRENT PREVENTION AND TREATMENT STRATEGIES FOR DN

Glucose and blood pressure control

In both type 1 and type 2 DM, strict control of blood glucose is crucial to contrast DN, for it both delays onset of proteinuria and reduces the rate of progression to ESRD. In the Diabetes Control and Complications Trial (DCCT), intensive insulin administration, either by continuous infusion with an external pump, or by multiple daily injections, resulted in a 60% reduction in the onset of microalbuminuria in type 1 DM patients vs. conventional treatment. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic control treatment produced a significant reduction in microvascular complications, and microalbuminuria risk decreased by one third, regardless of the primary treatment modality—insulin, sulfonylureas, or metformin, in type 2 DM patients (UKPDS Group, 1988). Data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) indicate that

intensive glycemic control is effective not only in reducing development and progression of albuminuria, but also in decreasing the risk of ESRD by 65% (Perkovic et al., 2013).

Antihypertensive drugs slow down onset and progression of DN (ADA, 2015) probably the result of the concomitant abatement of blood pressure in the glomerular capillaries. In meta-analysis studies (Palmer et al., 2015), the antihypertensive drugs that prove the most effective for this end are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Not only has long-term treatment with ACE inhibitors prevented development of microalbuminuria, but it has also exerted a survival benefit in patients with DN (Strippoli et al., 2015). The Heart Outcomes Prevention Evaluation (HOPE), as well as more recent studies, have shown that treatments with an ACE inhibitor and/or an ARB in patients with type 2 DM were the most effective strategies against ESRD (Sleight, 2000; Palmer et al., 2015).

Control of obesity and the metabolic syndrome

Obesity, a condition affecting an ever larger portion of the population in the Western world, has been related to renal dysfunction, even if the mechanisms of action at play are largely unknown (Wickman & Kramer, 2013). An interesting observation linking obesity to glomerulopathy is that the increasing prevalence of obesity is paralleled by an increase in the microscopic evidence of obesity-related glomerulopathy, from 0.2% in the ‘80s to 2.0% in the late ‘90s. Histologically, large-size glomeruli were seen in all specimens in the Columbia University series; focal and segmental glomerulosclerosis was also seen in 57 of 71 specimens (D’Agati et al., 2016). The focal and segmental glomerulosclerosis associated with obesity, however, differs from the idiopathic form of the disease because of a more indolent course, lower incidence of nephrotic syndrome, and milder foot process fusion and foot process loss seen in electron microscopy (Kambham et al., 2001). The glomerulopathy that is seen in association with any of the three classes (submorbid to

morbid) of obesity clinically entails proteinuria but does not progress to nephrotic syndrome (D'Agati et al., 2016).

The direct mechanisms of obesity-driven damage could include hyperfiltration, increased glomerular capillary-wall tension, and podocyte stress, which are, at least in part, reversed by weight loss. Moreover, altered levels of adipose tissue-derived adipokines can affect both glomerular filtration rate and permeability to proteins (Briffa et al., 2013). Additional, indirect mechanisms are obesity-mediated DM and hypertension (Wickman & Kramer, 2013).

The beneficial role of obesity correction to fend off renal damage is generally recognized. Either weight loss or captopril treatment was associated with reduction in proteinuria in a group of obese subjects (Praga et al., 1995). From a theoretical viewpoint, the hyperfiltration elicited by both DM and obesity suggests the hypothesis that obesity should facilitate inception of DN. A clinical study performed in Japan followed a large group of volunteers with normal kidney function over three years. Proteinuria developed in 5.8% of participants (6.7% in men and 4.4% in women), and was positively associated with body mass index at baseline. The relative risk for obesity was lower than that of hypertension, but significant for the development of proteinuria in males, irrespective of hypertension or DM co-morbidity (Tozawa et al., 2002). The gender differences highlighted in this study could be related to the different response of males and females to hyperfiltration. In fact, in the experimental setting, female estrogens effectively contrast renal lesions in the remnant tissue of subnephrectomized rats (Ji et al., 2005).

Obese patients with DN, treated with standard protocols for glycemic control and hypertension, showed significant reductions in both serum creatinine concentration and proteinuria level after a four-week formula low-calorie, normal-protein diet (Saiki et al., 2005). Obese patients with type-2 DM and DN receiving a low-calorie diet - protein content of 0.8 to 1.0 g/kg ideal body weight corresponding to a 20% energy deficit - underwent reduction in resistin, a possible obesity-related

mediator of insulin resistance, inflammation and microangiopathy in type 2-DM patients (Kozlowska et al., 2010).

Overweight patients with type-2 DM and chronic proteinuria were randomly assigned to a control group or to a study group receiving a 5-month diet with a daily energy reduction of 500 kcal and 1 to 1.2 g/kg/d protein. The diet group showed moderate weight loss and a significant decrease of proteinuria (2.9 to 1.9 g/24h). Similar results were also found in overweight patients with proteinuria of different origin (Kittiskulnam et al., 2014). Several studies have pointed out that overweight and frankly obese patients on hemodialysis enjoy better long-term survival expectations that normal weight or underweight patients. A tentative explanation of this apparently paradoxical finding is that obese patients are less likely to suffer from energy deficits, whereas underweight patients tend to recover more slowly from intervening illnesses (Ladhani et al., 2016).

The metabolic syndrome (MS) is defined as the cluster of central obesity plus at least two of the following metabolic abnormalities: high blood pressure, dysglycemia, high triglycerides and low high density lipoprotein (HDL) levels (Alberti et al., 2009). The MS is associated with an increased risk of cardiovascular disease (CVD) and chronic renal disease (CKD) in the general population and in patients with type 2 (Luk et al., 2008; Bonora, 2006) and type 1 DM (Thorn et al., 2009).

There is considerable evidence that obesity, hypertension and other elements of the MS contribute to the progression of renal disease independent of DM, although the way they interact to promote DN development is not completely understood (Maric & Hall, 2011). It is well established that subjects with MS experience higher rates of atherosclerosis, myocardial infarction and stroke than patients without MS (Bonora, 2006). There is also a positive correlation between number of MS traits and both CVD and CKD. What is more, CVD and CKD remain positively associated even after adjustment for the MS (Ferraro et al., 2011). Hence, more research is needed to understand and unravel the complexity of the relationship between CVD and DN.

Non-alcoholic fatty liver disease (NAFLD) is another medical condition associated with CVD and CKD, the prevalence of which is increasing worldwide in parallel with the increasing incidences of obesity and type 2 DM. Although a likely explanation for the associations between NAFLD, CVD and CKD is the sharing of common risk factors (i.e., the MS traits), growing evidence suggests a role for NAFLD, especially if steatohepatitis is present, in the development of atherosclerosis and kidney damage (Bonora & Targher, 2012). Therefore, lowering cardiometabolic and DN risk factors such as obesity, insulin resistence/dyslglycemia and chronic low grade inflammation through dietary intervention should be part of the global response to the epidemic of type 2 DM and related metabolic disorders.

DIETARY INTERVENTION IN DN

Dietary factors that could aggravate DN

High-salt, sugar, and fatty foods are known factors that favor progression of DN indirectly, through exacerbation of hypertension, hyperglycemia, dyslipidemia and obesity. In addition, the role of dietary proteins has been long considered and restricted intake has been commonly utilized to slow down DN progression. However, considerable attention has been recently paid to the glycotoxin content of food, which can directly affect renal function (Figure 1).

Protein intake

The beneficial role of low-protein diet, a standard dietary recommendation for most renal diseases, is debated in DN, especially in lesions related to type 2 DM (Pedrini et al., 1996; Otoda et al., 2014) (Table 1). On the one hand, clinical evidence suggests that dietary protein intake is

similar in diabetic patients with or without DN (Franz & Wheeler, 2003). On the other hand, the Modification of Diet in Renal Diseases (MDRD) Study supports the view that lower protein intake retards the progression of advanced renal disease (Levey et al., 1996). However, low-protein and very-low-protein diets, which are safe for two to three years, entail a risk of deterioration of the patient's nutritional status and protein calorie malnutrition (Noce et al., 2016).

In type 1 DM patients, a low-protein, low-phosphorus diet resulted in a slower decrease in creatinine and iothalamate clearance over a 3-year follow-up period (Zeller et al., 1991). A meta-analysis of dietary protein restriction (Pedrini et al., 1996) showed similar, beneficial effects both in insulin-dependent diabetic and non-diabetic patients with renal disease. In particular, in diabetic patients low-protein diet significantly slowed the increase in albumin level or the decline in GFR or creatinine clearance.

A four-year prospective trial in type-1 DM patients on a low-protein diet showed a significant reduction in progression to ESRD or death rate, but a decline of GFR similar to that of the control group composed of type 1 diabetic patients on unrestricted protein diet. The mechanisms underlying the protective effect of protein restriction remain unclear, also in consideration of the lack of significant differences between the two diet groups in terms of cardiovascular risk factors and pharmacological treatment (Hansen et al., 2002). In a two-year follow-up study, moderate protein restriction in the diet failed to prevent progression of the disease in type-1 or type-2 diabetic patients with incipient or overt DN (Dussol et al., 2005).

Additional data indicate that low-protein diet is not efficacious in type 1 and type 2 DM patients. A Cochrane review, based on 12 studies, concluded that protein restriction is ineffective in slowing down DN (Robertson et al., 2007), and a metanalysis of randomized controlled trials did not find change of GFR in type 1 and type 2 DM patients undergoing a low-protein diet (0.91 g/Kg BW/day vs a usual intake of 1.27 g/kg BW/day) (Pan et al., 2008). Another concern is that strict protein restriction requires considerable effort on the side of the patient, which often results in poor

compliance (Pijls et al., 2002). As a general consideration, reduction of protein intake must preserve adequate energy and nutrient intake.

A major issue is the composition of the protein intake, whether predominantly of vegetable, dairy or animal origin; it is also important to separate red meat, fish, or poultry as sources of animal proteins (Table 2). Considering that the effects of the different types of protein on the course of DN could also be ascribed, at least in part, to other nutrients from a given food source, we will discuss this issue later.

Glycotoxin ingestion

Accumulation of advanced glycation end-products (AGEs) is one of the most relevant event linking hyperglycemia and dyslipidemia to their vascular complications, including DN (Ahmed, 2005). AGEs derive from reactive carbonyl species (RCS), which accumulate due to increased formation via non-enzymatic glycation, glyco or lipoxidation or enzymatic metabolism, and/or to reduced disposal via hepatic detoxification or renal clearance. AGEs, which cause inflammation and oxidative stress in tissues, increase with age and, at an accelerated rate, in diabetic patients (Goldin et al., 2006), as shown by the rise in circulating indicators, such as N(ε)-carboxylethyl-lisine and methylglyoxal derivatives (Uribarri et al., 2007). Experimental data indicate that reactive oxygen species (ROS), which are produced at an increased extent in diabetes, promote the formation of endogenous AGEs (Nishikawa et al., 2000), which in turn favor progression of diabetes-induced renal damage through AGE-receptor-mediated mechanisms (Menini et al., 2007). The primary role of AGE-receptor-mediated mechanisms in DN is a relevant point since, in addition to being produced endogenously, AGEs are also generated in foods with cooking and industrial processing, which also reduce the nutritional value of their protein content (Rérat et al., 2002). Although the hazard of ingested AGEs for humans has been traditionally considered irrelevant, several recent

studies support the view that the diet is the main source of AGEs (Yubero-Serrano et al., 2015; Uribarri et al., 2005).

When an AGE-specific ELISA assay was employed to examine the effect of AGE-rich protein meal on the AGE serum and urine concentration (Koschinsky et al., 1997), a 200-fold increase in serum AGE immunoreactivity was found in volunteers fed a breakfast-time diet including egg whites cooked with fructose in comparison with another group fed egg white only. Only one-third of the absorbed AGEs appearing in the serum was detected over the ensuing 48h in the urine. The remarkable increase in AGE concentration, which occurred both in non-diabetic and diabetic subjects, confirmed the hypothesis that AGE moieties present in food survive the digestive process and are transported in the bloodstream in concentrations proportional to the amount fed. What is more, clinical and experimental data indicate that the oxidative stress and inflammation induced by AGEs can be managed by effective intervention to prevent AGE accumulation by either reducing AGE intake with food or an AGE-binding drug (Vlassara et al., 2002; Yubero-Serrano et al., 2015). This approach might be useful to combat the epidemics of MS and age-associated diseases, such as Alzheimer's disease (Vlassara et al., 2009; Uribarri et al., 2015; Cai et al., 2014), and also to prevent DM complications, including DN. Low dietary AGE content provided sustained protection towards DN development in experimental rodent models of both type 1 and 2 DM (Zheng et al., 2002). Studies on both non-diabetic and diabetic patients with kidney disease indicate that circulating AGE levels positively correlate with the amount of ingested AGEs and the severity of vascular and renal complications (Vlassara & Striker, 2011; Stinghen et al., 2016).

Finally, a randomized crossover study demonstrated that the Mediterranean diet is effective also in reducing serum levels of AGEs and increasing antioxidant defences compared with a Western diet regimen. After 4-week periods of Mediterranean diet, serum levels of methylglyoxal and N-carboxymethyllysine, the principal forms of AGEs, and peripheral mononuclear cell expression of the pro-inflammatoy receptor for AGEs (RAGE) were lower in subjects randomized

to the Mediterranean diet. Conversely, mRNA levels of glyoxalase I (GloxI), which is a critical enzyme in methylglyoxal detoxification, and of the anti-inflammatory AGE receptor-1 (AGER1), were higher in participants assigned to the Mediterranean regimen (Lopez-Moreno et al., 2016).

DIETARY FACTORS THAT COULD AMELIORATE DN

Macronutrients

Several studies have looked into the effect of changes in the dietary habits that could have positive effects on DN and, in general, on the mechanisms of DM complications. A peculiar characteristic of them is that the ethnic background of the researches has influenced the type of food investigated.

A Portuguese-British group has examined a group of healthy volunteers from Glasgow receiving a daily supplement of 20 mL of uncooked olive oil, either of low fenolic (refined oil) or high-fenolic (extra-virgin oil) content for six weeks. Olive oil supplement led to a significant improvement in the proteomic coronary artery disease score; what is more, both oil type consumed were associated with positive changes in the urinary proteomic biomarkers and other indicators such as triacylglycerols, oxidized LDL, and LDL cholesterol (Silva et al., 2015).

A Spanish multicentre randomized trial investigated the effect of olive oil as a dietary approach to reduce the progression of diabetic complications. A total of 7,447 healthy participants at high cardiovascular risk, of which 3,614 were diabetics, were randomized to receive a Mediterranean diet supplemented with extra-virgin olive oil as main source of monounsaturated fat, or were advised to reduce dietary fat (control group). Diabetic and non-diabetic participants assigned to the Mediterranean diet supplemented with extra-virgin olive oil reduced the incidence of major cardiovascular events compared with the control group, with an hazard ratios of 0.71 (95%

confidence interval [CI], 0.53 to 0.96) and 0.67 (95% CI, 0.45 to 1.01), respectively, versus the control group (Estruch et al., 2013). In the same study, similar protective effects were also obtained with a Mediterranean diet supplemented with mixed nuts.

A Swedish study addressed the effect of fish protein. Young type 1 DM patients, consuming a mean of 9.3 g of fish protein per day (equivalent to 53 g of fish), had lower odd ratios for microalbuminuria in comparison with those assuming less fish protein (mean 2.7 g per day, corresponding to 15 g of fish). A higher rate of microalbuminuria was also found in the same study in diabetic patients with lower milk intake; high milk protein intake was almost as significantly protective as fish protein against microalbuminuria, although part of milk protection might be ascribed to an age-dependent effect (Mollsten et al., 2001). In the above mentioned Swedish study, the positive effect of fish consumption on prevention of microalbuminuria, however, could also be attributed, at least in part, to fat or other fish components. The role of n-3 polyunsaturated fatty acids, which may be beneficial in different renal diseases, is highly debated for DN (De Caterina et al., 2007), in particular for progression of microalbuminuria. A peculiar observation is that a prospective study on diabetic patients receiving a dietary supplementation of n-3 polyunsaturated fatty acids (4.6 g of n-3 fatty acids per day) for one year in comparison with controls receiving olive oil as placebo showed that the olive oil did reduce progression of albuminuria while n-3 fatty acids was ineffectual (15% progression for olive oil vs. 25% for n-3 fatty acids) (Rossing et al., 1996). These data are in keeping with those on olive oil published in the Portuguese-Scottish and Spanish studies above.

Another cross-sectional study from Brazil has investigated the effects of polyunsaturated fatty acids and proteins in type 2 DM patients. Patients with microalbuminuria had higher intake of protein than normoalbuminuric patients; conversely, consumption of polyunsaturated fatty acids from vegetable sources, plant oils, and margarines was higher in normoalbuminuric patients. These differences persisted after multivariate logistic regression analysis to adjust for gender, age,

presence of hypertension, and levels of fasting glucose (Almeida et al., 2008). From these data, however, it is difficult to attribute a direct positive effect of polyunsaturated fatty acids on DN, as well as a harmful effect of the proteins as such. In fact, the same research group had previously published data from a randomized cross-over trial showing that a normoproteic diet with chicken as primary source of protein reduced GFR in normoalbuminuric type 2 DM patients and was more effective than a low protein diet in reducing urinary albumin excretion rate in microalbuminuric individuals (Gross et al., 2002).

Still in relation to the issue of the type of proteins, a group of ESRD patients with inflammation, an important predictor of morbidity and mortality because of its association with poor nutrition status and accelerated CVD, received a protein supplement drink consisting of isoflavone-rich soy beans during each session of dialysis. Blood levels of isoflavones correlated negatively with markers of inflammation such as C-reactive protein, and positively with markers of nutrition. These data suggest the possibility of beneficial effects of isoflavone-rich soy food in ESRD (Fanti et al., 2006). Finally, a Japanese group has compared the effect of the ingestion of either tuna fish (0.7 g/kg body weight of protein), or boiled egg white (0.7 g/kg or 1.4 g/kg body weight of protein). Tuna fish was associated with a significant rise in the GFR, both in non-diabetic and in diabetic volunteers. This finding was ascribed to the increase in glycin and alanin concentration in the plasma, and the increased excretion of 6-keto-prostaglandin F1α related to tuna fish meal (Nakamura et al., 1993).

Micronutrients

Clinical data in humans

Beyond the above considerations on macronutrients, considerable attention has also been dedicated to the role of micronutrients in DN. Lipoic acid and its reduced form, dihydropiloic acid, because of their antioxidant properties are suited to prevent and treat diabetic complications related to AGE

accumulation. In fact, lipoic acid has been shown to increase glucose uptake by plasma membranes through recruitment of glucose transporter-4, a mechanism shared with insulin; moreover, dihydrolipoic acid scavenges superoxide and peroxyl radicals, and facilitates vitamin E recycling (Packer et al., 2001). Lipoic acid occurs naturally in various meat products, and vegetables. However, the bioavailability of lipoic acid contained in natural food is minimal (Reed, 2001). In addition to experimental studies that will be discussed below, an Iranian study has investigated the effects of lipoid acid-plus-pyridoxine (vitamin B6) in patients with type-2 DM with albuminuria. Such supplementation resulted in significant decrease in albumin excretion. This finding was ascribed to both substances, as previously observed in the experimental setting, possibly via a decrease in oxidative and carbonyl stress (Noori et al, 2013). However, two 24-week, multicenter, phase-2 trials investigating the effects of the administration of lipoic acid alone showed lack of efficacy on albuminuria (Morcos et al., 2001). Similarly, pyridoxamine alone in patients with type 1 and type 2 diabetes and overt nephropathy was not able to decrease albuminuria, though it significantly reduced urinary transforming growth factor beta1 (TGF-β1), AGEs and the change from baseline in serum creatinine (Williams et al., 2007).

Sulforaphane, a bioactive compounds contained in broccoli sprouts, has the potential to activate the nuclear factor erythroid-derived 2-related factor-2-dependent antioxidant response –signaling pathway, attenuates oxidative stress, induces phase 2 enzymes, and reduces inflammation by inactivation of nuclear factor (NF) κB. In type 2 diabetic patients, broccoli sprout administration increase total antioxidant capacity of plasma and decrease oxidative stress and lipid peroxidation. Assumption of sulforaphane through broccoli sprout supplementation of diet in type-2 diabetics is likely to attenuate DN and vascular complications (Bahadoran et al., 2013).

Experimental data in rodent models of diabetes

Several natural compounds contained in foods have been tested for their ability to slowdown the progression of renal injury in rodent models of diabetes. A definite molecular mechanism of protection has not been fully elucidated for all of these substances. However, for simplification purposes, we have divided the compounds in two categories based on the reported literature data on their chemical properties.

Antioxidant and anti-inflammatory compounds

In an experimental setting, 7-month treatment of diabetic rats with lipoic acid resulted in prevention or attenuation of albuminuria, TGF-β1, and glomerulosclerosis. In the renal cortex, levels of glutathione were higher and accumulation of malondialdehyde lower than in diabetic controls. What is more, insulin-treated rats enjoyed better glycemic control, but showed significant deterioration in renal function, a finding suggesting that the renoprotective effect of lipoic acid should be ascribed to its antioxidant properties (Melhem et al., 2002).

Purple corn, which is rich in anthrocyanins, decreased expression of endothelial vascular cell adhesion molecule-1, E-selectin, and monocyte integrins-ß1 and -ß2 through blocking the mesangial tyrosine kinase 2 pathway in human endothelial cells and THP-1 monocytes cultured in conditioned media exposed to 33 mM glucose. In the glomeruli of diabetic kidneys, purple corn extract attenuated induction of intracellular cell adhesion molecule-1 and CD11b. It also decreased monocyte chemoattractant protein-1 expression and macrophage inflammatory protein 2 transcription in the kidney (Kang et al., 2012).

Ellagic acid, the dilactone of hexahydroxydiphenic acid, is a natural phenol antioxidant found in oaks species and in several edible fruits such as berries, pomegranate, walnut and pecan nuts. In diabetic rats administered ellagic acid supplement for 16 weeks, activation of renal NFκB, a major mediator of the inflammation associated with DN, was significantly inhibited. Kidney lesions were reduced, whereas tissue with TGF-β1 and fibronectin expression was suppressed. In tubular cell

cultures, ellagic acid also inhibited high-glucose-induced activation of NFκB and pro-inflammatory cytokine synthesis (Ahad et al., 2014).

Inhibitors of AGE formation

Pyridoxamine, a *vitamer* belonging to the B6 family, is naturally found in fish, chicken, eggs, walnuts and other foods. It has been shown to be effective to inhibit AGE formation, and to prevent the rise of plasma creatinine levels, albuminuria, and glomerular hypertrophy in rats with streptozotocin-induced type 1 DM (Degenhardt et al., 2002). Recently, pyridoxamine has proved effective to prevent the onset of albuminuria and glomerular lesions also in type 2 diabetic db/db mice, and, in combination with enalapril, to reduce mortality and progression of established DN. Interestingly, the protective effect of pyridoxamine paralleled a decrease in AGE levels in diabetic db/db mice (Zheng et al., 2006).

L-carnosine (β-alanyl-L-histidine), a histidine containing dipeptide commonly found in the nervous system and skeletal muscle, serves as a major endogenous quencher of RCS (Aldini et al., 2005), a heterogeneous class of highly reactive compounds derived from oxidation of lipids and carbohydrates which react with proteins to generate AGEs (Ahmed, 2005). Unfortunately, L-carnosine has a short half-life in humans, because it is rapidly inactivated by serum and tissue carnosinase. The shortest allelic variant of the serum carnosinase CNDP1 gene was shown to be associated with protection against DN (Janssen et al., 2005). In fact, the shortest allelic variant determines lower enzyme levels and activity than longer variants (Riedl et al., 2007). The resulting higher L-carnosine levels is reputed to exert a more effective detoxifying action, a fact that could explain its protective effect against DN. These data have been confirmed in experimental models of DN in rodents that suggest the view that carnosinase-resistant derivatives of carnosine exert a beneficial effect on DN through reduction of (a) circulating AGEs, (b) their tissue accumulation, and (c) related inflammation (Menini et al., 2015). From a nutritional point of view, usual protein-

rich staples of the western diet, such as fish and meat, in particular poultry, are major sources of carnosine (Kohen et al., 1988).

CONCLUSIONS

The most effective strategies to prevent development and progression of DN consist of (i) achieving good glycemic control with anti-diabetic medications and lifestyle modification, (ii) treating hypertension with drugs blocking the renin angiotensin-aldosterone system, and (iii) favoring weight loss in overweight and obese patients through a low-calorie diet, which is also effective in improving the lipid profile. Despite the number of publications regarding the diet approach to contrast DN, no consensus has been reached on a treatment protocol. The following are the main considerations stemming from this review:

(1) The major area for possible diet intervention is protein intake. An unselected reduction of protein intake with the diet in diabetic patients with the purpose of delaying DN onset or reducing its progression is questionable and in some instances has proved to be counterproductive. The source of protein is probably the best contender for the dietary modulation of renal damage. For instance, a diet ensuring a normal amount of protein with chicken as its only source, or a protein supplement of isoflavone-rich soy beans, may represent an additive strategy for prevention and treatment of patients with type 2 DN. The mechanisms underlying these positive effects, although still unproven, could be attributed to associated micronutrients contained in these foods, which contribute to improve lipid profile, reduce AGE accumulation, and/or reduce the chronic low-grade inflammation characterizing DM (Figure 2).

(2) The AGE content of food, which in the past had been rejected as a possible basis for AGE-related renal damage, is now considered a major player in DN onset and progression. Reducing or

excluding food sources rich in AGE entails educational campaigns to foster healthy habits for food preparation, e.g., avoiding high-temperature cooking, and consumption. Accordingly, a new dietary AGE (dAGE) database was published in the Journal of the American Dietetic Association, which provides a valuable instrument to estimate dAGE intake and to indicate food choices to reduce dAGE intake (Uribarri et al., 2010).

(3) In the realm of micronutrient in the diet, the efficacy of functional foods should be tested in randomized clinical trials. A case in point is the selection of foods containing nutrients that could contrast the damaging events of DN, such as oxidative and carbonyl stress that govern AGE formation and accumulation, as well as the ensuing inflammation. So far, many compounds occurring naturally in various meats and vegetables have been tested in experimental models and, on occasion, in humans. Promising results have been obtained with the antioxidants and AGE inhibitors lipoic acid and pyridoxine, a form of the vitamin B6, which, in combination, have been shown to reduce albumin excretion in type-2 DM patients with albuminuria. Moreover, experimental data indicate the protective effects of the histidine-containing dipeptide, AGE-inhibitor, carnosine. An interesting observation is that this compound is particularly abundant in chicken, meat which has been shown to be protective in type 2 DM normoalbuminuric and microalbuminuric patients. These considerations suggest that search and test for carnosine derivatives resistant to the enzyme carnosinase may represent a suitable strategy against DN.

(4) Some diet adjustments, at worst innocuous, such as addition of olive oil to the standard diet and the consumption of brassicaceae, anthocyanin and ellagic acid-rich food, appear promising.

A final consideration is that a number of specific foods or natural compounds contained in foods, most of which are exotic and used in traditional medicine, have shown some beneficial effects in experimental models of DN or in the clinical setting. These data are not reviewed in this work because in our view adequate information on the mechanisms at play and/or robust preclinical and clinical data are lacking.

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Conflicts of interest

None

Author contributions

S.M. and C.P. conceived the study, performed a systematic literature search for records to be included in the review and drafted the article. C.I. and G.P. revised the article critically and suggested pertinent changes. All Authors have approved the final article.

List of abbreviations

ACE = angiotensin-converting enzyme; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AGEs = advanced glycation end-products; AGER1 = AGE receptor-1; ARB = angiotensin II receptor blocker; CI = confidence interval; CKD = chronic renal disease; CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; dAGE = dietary AGEs; DM = diabetes mellitus; DN = diabetic nephropathy; ESRD = end-stage renal disease; GFR = glomerular filtration rate; GloxI = glyoxalase I; HDL = high density lipoprotein; HOPE = Heart Outcomes Prevention Evaluation; KDIGO = Kidney Disease: Improving Global Outcomes; MDRD = Modification of Diet in Renal Diseases; MS = metabolic syndrome; NAFLD = non-alcoholic fatty liver disease; NFκB = nuclear

factor κB; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; RCS = reactive carbonyl species; ROS = reactive oxygen species; TGF-β1= transforming growth factor beta1; UKPDS = United Kingdom Prospective Diabetes Study.

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Table 1

Studies investigating the effects of dietary protein restriction on the progression of DN

Authors, year	Number, type of patients, type of study	Protein intake	Major results
Zeller et al., 1991	35, Type 1 diabetes, randomized prospective trial	0.6 g/Kg BW	slower decrease of renal function
Pedrini et al., 1996	Type 1 diabetes, meta-analysis of 5 studies	From 0.50 to 0.85 g/kg BW	slower decrease of GFR and slower increase in urinary albumin excretion
Hansen et al., 2002	82, Type 1 diabetes, randomized prospective trial	0.89 g/kg BW	reduced risk of ESRD or death
Dussol et al., 2005	63, Type 1 and 2 diabetes, randomized prospective trial	0.8 g/kg BW	no protective effects on GFR and urinary albumin excretion
Robertson et al., 2007	Type 1 and 2 diabetes, Cochrane review of 12 studies	from 0.7 to 1.1 g/kg BW	no significantly slower progression to renal failure
Pan et al., 2008	Type 1 and 2 diabetes, meta-analysis of 8 studies	0.91 g/kg BW (average of the 8 studies)	no significant improvement of renal function

BW= body weight; ESRD= end stage renal disease; GFR= glomerular filtration rate

Table 2

Studies investigating the effects of different sources of proteins on chronic kidney disease

Authors, year	Number, type of patients, type of study	Protein source	Major results
Nakamura et al., 1993	6 healthy volunteers and 6 diabetic patients, comparative study	tuna fish/egg white	increased GFR after tuna fish ingestion in both healthy and diabetic subjects
Mollsten et al.,2001	1,150 Type 1 diabetes patients, nested case control study	fish/ milk	lower risk of microalbuminuria
Gross et al., 2002	28 Type 2 diabetes, randomized cross-over trial	chicken	lower microalbuminuria
Fanti et al., 2006	25 end stage renal disease patients, pilot study	soy food	reduced systemic inflammation and improved nutritional status

GFR= glomerular filtration rate

Figure Legends

Figure 1.

Main dietary factors promoting progression of diabetic nephropathy.

Relationship (dashed arrows) between dietary factors (rectangular boxes) and risk factors (oval boxes) for DN.

Figure 2.

Main protective factors against diabetic nephropathy.

Bold indicates the micronutrients which have only been tested in experimental studies. * Plant and animal foods.